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Desymmetrizing Hydroformylation with the Aid of a Planar Chiral Catalyst-Directing Group

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Hydroformylation of alkenes belongs to the most important industrially applied processes that rely on homogeneous catalysis.[1] A difficult problem is the control of stereochemistry throughout the course of this reaction. Despite significant advances employing asymmetric catalysis with chiral phosphorus ligands, this approach is limited to a restricted number of substrates.[2] An alternative approach makes use of substrate-bound catalyst-directing groups (CDG), which allow for diastereoselective hydroformylation of chiral substrates (Scheme 1, A).[3−5] However, if prochiral substrates were to be employed, the chirality information would have to reside in the catalyst-directing group. We herein report on a desymmetrizing hydroformylation of prochiral bisalkenyl-carbinols **1** (n = 0) and bisallylcarbinols **2** (n = 1) employing a new planar chiral catalyst-directing group (*o*-DPPF) (Scheme 1, B).

From previous investigations we know that attachment of the *ortho*-diphenylphosphanyl group (*o*-DPPB) to the alcohol function of an allylic or homoallylic alcohol substrate allows for diastereo- and regioselective hydroformylation due to efficient diastereotopic alkene face discrimination.[5] Control experiments established that the *o*-DPPB function exhibits the ideal geometry and donor properties to direct a rhodium catalyst efficiently into an allylic and homoallylic position of the corresponding substrate. Hence, it was envisioned that a planar chiral variant of the *o*-DPPB group such as the *ortho*-diphenylphosphanylferrocene carbonyl (*o*-DPPF) function may allow efficient stereodiscrimination of prochiral substrates. As particularly attractive substrates, symmetrical bisalkenylcarbinols **1** (n = 0) and bisallylcarbinols **2** (n = 1) were selected since a stereoselective monohydroformylation would set two stereogenic centers simultaneously to give potentially interesting chiral building blocks for polyketide synthesis. Stereoselective hydroformylation of these substrates is particularly challenging since diastereotopic alkene group discrimination and diastereotopic alkene face discrimination have to be managed simultaneously.[6]

Since symmetrical bisalkenylcarbinols of type **1** are rarely found in the literature, we developed simple access to **1a**−**e** following the routes depicted in Scheme 2. The bisallylcarbinols **2a**−**e** were obtained in a similar fashion upon addition of allyl Grignard or allyl zinc reagent to ethylformiate.[7]

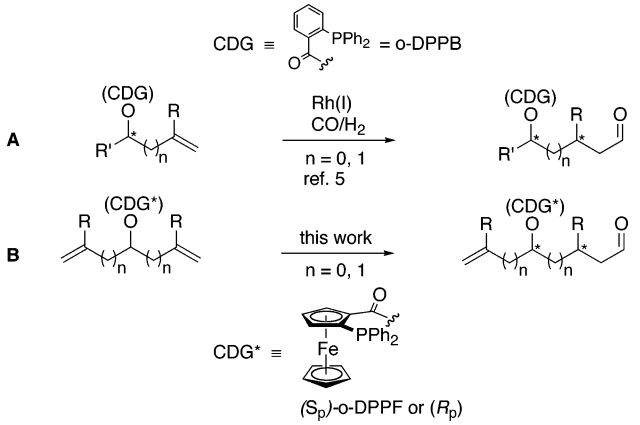
The subsequent esterification with the *ortho*-diphenylphosphanylferrocene carboxylic acid (*o*-DPPFA)[8] proved difficult, employing standard esterification protocols presumably due to severe sterical hindrance. Finally, good results were obtained upon activation of the carboxylic acid with BOP[9] and activation of the alcohol as the sodium or lithium alcoholate (Table 1).

Subjection of bisalkenylcarbinol *o*-DPPF esters to hydroformylation conditions (Table 2) furnished the *syn*-aldehydes **5** as the major product in good to excellent diastereoselectivity and in enantiomerically pure form. Thus, of the four possible diastereomeric monoaldehydes, *syn*-**5** is formed with high selectivity. The configuration of the major diastereomer was unequivocally determined through X-ray crystal structure analysis of aldehyde *syn*-**5a**.[7] Hence, a good diastereotopic alkene face discrimination concomitant with excellent diastereotopic alkene group discrimination was achieved. As can be seen from entries 1−5, diastereotopic face discrimination is somewhat influenced by the steric demand of the 2-substituent at the alkene, which may be due to increased 1,2-allylic strain.[10]

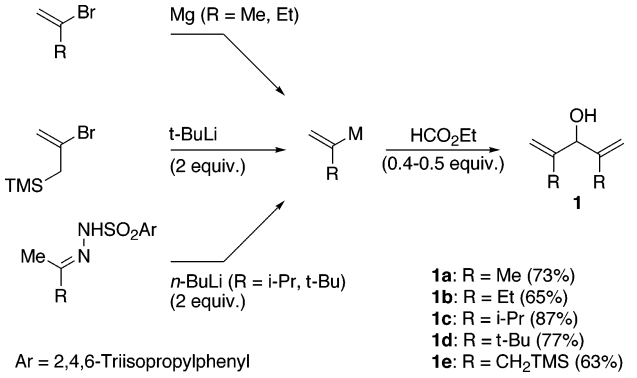
In the case of bisallylcarbinol-*o*-DPPF esters **4**, hydroformylation proceeded at milder conditions (Table 3) to give the *anti*-aldehydes **6** in good yield, excellent anti/syn-diastereoselectivity and in enantiomerically pure form. Here again efficient diastereotopic face discrimination concomitant with excellent diastereotopic group discrimination was achieved.[11]

Removal of the substrate-bound catalyst-directing *o*-DPPF group was achieved through saponification after protection of the aldehydes as the dimethylacetal. The alcohols **7** and **8** were obtained in good yields, and the *o*-DPPFA could be recovered. Alternatively, clean reductive removal of the *o*-DPPF group is achieved upon

Scheme 1. Concept of Desymmetrizing Hydroformylation with the Aid of *o*-DPPF as a Planar Chiral Substrate-Bound Catalyst-Directing Group (CDG*)

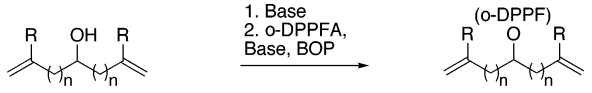


Scheme 2. Preparation of Bisalkenylcarbinols



10.1021/ja0467364 CCC: $27.50

Table 1. Preparation of Bisalkenyl- and Bisallylcarbinol *o*-DPPF Esters **3** and **4**



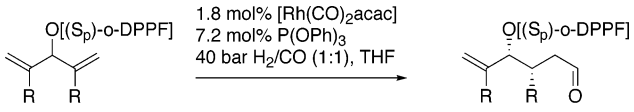
1: n=0
2: n=1

3: n=0
4: n=1

entry	R	*n*	*o*-DPPFA	base	product	*ee*[a] (%)	yield (%)
1	Me	0	(S_p)-	NaH	**3a**	>99	68
2	Et	0	(S_p)-	NaH	**3b**	>99	70
3	*i*-Pr	0	(S_p)-	NaH	**3c**	>99	65
4	*t*-Bu	0	(S_p)-	*t*-BuLi	**3d**	>99	75
5	CH_2TMS	0	(S_p)-	*t*-BuLi	**3e**	>99	80
6	Me	1	(R_p)-	NaH	**4a**	>99	61
7	Et	1	(R_p)-	NaH	**4b**	>99	85
8	*i*-Pr	1	(R_p)-	NaH	**4c**	>99	93
9	Ph	1	(R_p)-	NaH	**4d**	nd[b]	69
10	CH_2OTBS	1	(R_p)-	NaH	**4e**	>99	83

[a] Determined by HPLC. [b] Not determined.

Table 2. Desymmetrizing Hydroformylation of Bisalkenylcarbinol *o*-DPPF Esters **3**

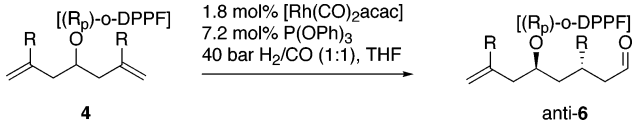


3 syn-**5**

entry	R	*T* (°C)	*t* (h)	conversion (%)	product	yield (%)[a]	dr[b] syn/anti	*ee*[c] (%)
1	Me	70	48	quant.	**5a**	90	88:12	>99[d]
2	Et	70	48	quant.	**5b**	80	93:7	>99[d]
3	*i*-Pr	70	48	95	**5c**	80	>98:2	>99[e]
4	*t*-Bu	90	72	61	**5d**	82[f]	>99:1	>99[e]
5	CH_2TMS	60	96	56	**5e**	71[f]	>99:1	>99[e]

[a] Isolated yield after chromatographic workup. [b] Determined by NMR of the crude reaction mixture. [c] Determined by HPLC after reduction to the corresponding primary alcohols with $NaBH_4$. [d] Refers to major and minor diastereomer. [e] Major diastereomer. [f] Based on recovered starting material.

Table 3. Desymmetrizing Hydroformylation of Bisallylcarbinol *o*-DPPF Esters **4**



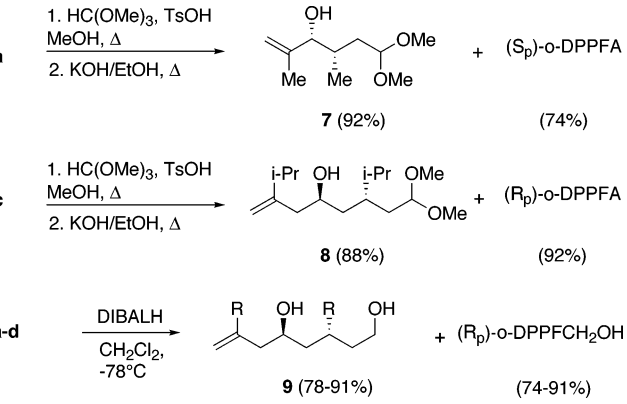
4 anti-**6**

entry	R	*T* (°C)	*t* (h)	conversion (%)	product	yield (%)[a]	dr[b] anti/syn	*ee*[c] (%)
1	Me	50	21.5	91	**6a**	83[d]	96:4	>99[e]
2	Et	50	21	83	**6b**	85[d]	95:5	>99[e]
3	*i*-Pr	60	24	81	**6c**	84[d]	87:13	>99[e]
4	Ph	70	24	82	**6d**	90[d]	94:6	>99[e]
5	CH_2OTBS	50	16	quant.	**6e**	80	95:5	>99[f]

[a] Isolated yield after chromatographic workup. [b] Determined by NMR of the crude reaction mixture. [c] Refers to major diastereomer. [d] Based on recovered starting material. [e] Determined by GC or HPLC after DIBAL reduction to the corresponding 1,4-diols **9** (see Scheme 3). [f] Determined by HPLC after reduction to the corresponding primary alcohols with $NaBH_4$.

DIBAL reduction. In summary, with the aid of a chiral substrate-bound catalyst-directing group, desymmetrizing hydroformylation of bisalkenyl- and bisallylcarbinol derivatives could be achieved

Scheme 3. Removal and Recovery of the Catalyst-Directing *o*-DPPF Group



with excellent levels of stereocontrol. Removal and recovery of the catalyst-directing *o*-DPPF group is possible and gives access to interesting chiral building blocks in enantiomerically pure form. Furthermore, this stereoselective hydroformylation may be incorporated as a key step for synthetically interesting Tandem processes.[5,12]

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Supporting Information Available: Experimental details (PDF) and X-ray crystal structure details (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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